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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/328,130 | 06/08/99 | SELDEN R | 50010/007006 |

HM12/0117

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| EXAMINER | |
|---|---|
| SCHWARTZMAN, R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | 8 |

**DATE MAILED:** 01/17/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/328,130 | Applicant(s) Selden et al. |
|---|---|---|
| | Examiner Robert Schwartzman | Group Art Unit 1636 |

☒ Responsive to communication(s) filed on *Oct 26, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *108-189* is/are pending in the application.

Of the above, claim(s) *186-189* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *108-185* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

This Office action is in response to the Reply to Restriction Requirement filed October 26, 2000. Claims 108-189 are pending in this application.

### *Specification*

The abstract of the disclosure is objected to because it contains more than one paragraph. Correction is required. See MPEP § 608.01(b).

The specification contains nucleic acid and amino acid sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. Applicant must provide a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office action must include a complete response to the requirement for a new Sequence Listing.

***Election/Restriction***

Applicant's election without traverse of Group I, claims 108-185 in Paper No. 7 is acknowledged.

Claims 186-189 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 7.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 128-131 and 159-184 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 128-131 and 159-184 are vague and indefinite for recitation of the phrase "a heterogenous cell strain of secondary cells" because a strain is not a number of cells, rather it is a pure isolate of a type of cell. The rejection would be obviated by amending the claims to recite "a mixed population of cells consisting of two or more different cells strains of secondary cells".

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 108-185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Osborne *et al.* (Proc. Natl. Acad. Sci. USA (1988) 85:6851) or Palmer *et al.* (Blood (1989) 73:438) each in view of Skoultchi (WO 91/0666) and further in view of Browne *et al.* (Cold Spring Harbor Symposia Quant. Biol. (1986) LI:693).

Osborne *et al.* teaches (entire document) the isolation of primary human fibroblasts from patients with purine nucleotide phosphorylase (PNP) deficiency and the infection of these cells with a retroviral vector encoding PNP and a selectable marker. Palmer *et al.* teaches (entire

document) the isolation of human diploid fibroblasts and the infection of these cells with a retroviral vector encoding human clotting factor IX and a selectable marker. The fibroblasts expressing factor IX were administered to nude mice and circulating factor IX was detected (page 442, column 1, first full paragraph). Osborne *et al.* or Palmer *et al.* do not teach cells comprising DNA encoding EPO or delivery of the DNA into the cell by transfection. Skoultchi teaches the introduction of DNA encoding a heterologous protein along with a selectable marker into primary or secondary cells. The primary cell may be any mammalian cell of interest, including fibroblasts, lymphocytes, epithelial cells, neurons and endothelial cells (page 4, line 30-page 5, line 4). DNA is introduced into the primary cell for the purpose of homologous recombination (page 4, lines 6-29). The DNA can be introduced into the cell by calcium phosphate precipitation, microinjection, electroporation, polycations or viral vectors (page 8, line 29-page 10, line 9). Once the primary cell is transfected clonal cell lines can be developed from cells which have been identified as having undergone homologous recombination (page 14, lines 3-14). Browne teaches the gene encoding EPO and the usefulness of the recombinant EPO protein for therapy of diseases in which red blood cell counts are low (page 699). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate primary human fibroblasts and introduce a gene encoding a potential therapeutic protein of interest as taught by Osborne *et al.* or Palmer *et al.* and to use this system to express EPO as taught by Browne, motivated by the teachings of Osborne *et al.* or Palmer *et al.* that primary fibroblasts can be used to express heterologous proteins both *in vitro* and *in vivo* and that the primary fibroblasts can be

used to study the effect of expressing potential therapeutic proteins *in vivo* and the teaching of Browne that EPO is an important therapeutic protein. One of ordinary skill in the art would reasonably expect that primary fibroblasts which have been shown to express different heterologous proteins would be equally likely to express EPO at a level sufficient to study the effect of recombinant EPO expression in animal models. Furthermore, a general motivation existed in the art to study the effect of heterologous gene expression *in vivo* for the purpose of elucidating possible therapeutic methods. It would further have been *prima facie* obvious to one of ordinary skill in the art to introduce a heterologous gene into primary fibroblasts by any available method based on the teaching of Skoultchi that a variety of methods can be used to deliver DNA into primary cells and the exemplification of electroporation as one viable method. One would reasonably expect that the ability of a primary cell to express a heterologous protein would be independent of the method by which the DNA is stably incorporated into the cell.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 108-185 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 135-199 of copending Application No. 09/354,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is drawn to primary or secondary cells comprising a nucleic acid encoding a protein and methods of producing the cells, wherein the present claims are limited to EPO while the claims of 09/354,883 are drawn to any therapeutic product. One of ordinary skill in the art would instantly be aware that EPO is a therapeutic product, thereby rendering the narrow claims obvious over the broader claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 108-185 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 5,994,127. Although the conflicting claims are not identical, they are not patentably distinct from each other because the EPO delivery composition and method of producing the composition of 5,994,127 necessarily comprises the cells and methods of producing the cells of the present claims.

Claims 108-185 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,048,524. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of delivering EPO to a mammal of 6,048,524 necessarily comprises the cells and methods of producing the cells of the present claims.

Claims 108-185 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,048,729. Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is drawn to primary or secondary cells comprising a nucleic acid encoding a protein and methods of producing the cells, wherein the present claims are limited to EPO while

the claims of 6,048,729 are drawn to any therapeutic protein. One of ordinary skill in the art would instantly be aware that EPO is a therapeutic protein, thereby rendering the narrow claims obvious over the broader claims.

Claims 108-185 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 6,054,288. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of delivering a therapeutic product to a mammal of 6,054,288 necessarily comprises the cells and methods of producing the cells of the present claims. One of ordinary skill in the art would instantly be aware that EPO is a therapeutic product, thereby rendering the narrow claims obvious over the broader claims.

Claims 108-185 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,063,630. Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is drawn to primary or secondary cells comprising a nucleic acid encoding a protein and methods of producing the cells, wherein the present claims are limited to EPO while the claims of 6,063,630 are drawn to any therapeutic product. One of ordinary skill in the art would instantly be aware that EPO is a therapeutic product, thereby rendering the narrow claims obvious over the broader claims..

***Conclusion***

Claims 108-185 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz, can be reached at (703) 308-1133. The fax number for this group is (703) 305-3014.

Any inquiry of a administrative or procedural nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, Patent Analyst, whose telephone number is (703)-305-3388.

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

January 15, 2001

Application No. 09/378,130

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

**Applicant must provide:**

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

**Please return a copy of this notice with your response.**

09/328,130
Attach # 8

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FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:24:25 ON 14 JAN 2001

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L1         50710 S ERYTHROPOIETIN OR EPO
L2         23906 S L1 NOT PY>1992
L3       8269382 S CELL OR CELLS
L4       1014767 S FIBROBLAST? OR KERATINOCYTE? OR EPITHELIAL OR ENDOTHELIAL
L5       1940010 S GLIAL OR NEURAL OR LYMPHOCYTE? OR HEPATOCYTE?
L6       1328231 S MUSCLE OR MYOBLAST? OR MYOTUBE? OR MYOCYTE?
L7       1991540 S PRIMARY OR SECONDARY
L8        131198 S L7 (4A) L3
L9         23401 S L7 (4A) L4
L10        33018 S L7 (4A) L5
L11        11138 S L7 (4A) L6
L12       177254 S L8 OR L9 OR L10 OR L11
L13          154 S L2 AND L12
L14           77 DUP REM L13 (77 DUPLICATES REMOVED)
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